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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,162	04/07/2000	ANTHONY P. SHUBER	EXT-026	1013

7590 11/19/2001

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EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1655	9

DATE MAILED: 11/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/545,162	LAPIDUS ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 7-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This action is written in response applicant's correspondence submitted 8/27/01, paper number 8. Claim 7 has been amended, claims 1 and 6 have been canceled, and claims 8 and 9 have been added. Claims 2-5 and 7-9 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The application recites nucleic acid sequences, but there is no sequence listing or CRF on file (see, for example, pages 15 and 16).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit a CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

3. Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 depend from rejected claims, therefore the subject matter encompassed by these claims is unclear.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for screening a patient for colorectal cancer or precancer by determining in fecal matter a ratio between a first amount of long nucleic acid of a length greater than 200 base pairs and a second amount of nucleic acid of a length less than said long nucleic acid, does not reasonably provide enablement for the detection of other types of cancer or precancer or the use of tissues or body fluids other than fecal matter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is drawn to encompass the identification of patients having any cancer or precancer by determining, in any body fluid or tissue comprising exfoliated cells, the ratio of long nucleic acids versus short nucleic acids. The specification demonstrates the method using a fecal matter sample for the screening of a patient for colorectal cancer or precancer by detecting the amount of three different long nucleic acid molecules (p53, K-ras, and apc). The specification demonstrates that for these three molecules PCR products of longer than 200 base pairs were present in the fecal matter of patients with colorectal cancer or precancer but such fragments were not present in healthy patients (Example 1). Neither the specification nor the prior art demonstrate that such a relationship exists for other cancers or for other body fluids.

The level of unpredictability for the detection of any disease using a nucleic acid assay is quite high. Since neither the specification nor the prior art provide any evidence of a universal association between a ration of nucleic acids greater than 200 base pairs to nucleic acids shorter than 200 base pairs and every cancer and every body fluid, a practitioner wishing to practice the claimed invention would be required to provide the extensive experimentation necessary to demonstrate such an association. Such experimentation would in itself be inventive.

In light of the lack of guidance in the specification and the prior art, and in light of the high level of unpredictability in the instant subject matter, it is concluded that undue experimentation would be required to practice the instant invention commensurate in scope with the claimed invention.

It is noted that the claims that are present in allowed patent US 6143529 are of very similar scope to the instantly claimed invention. The instant rejection is not intended to call into question the validity of these claims because the claims in the '529 patent were allowed over a declaration which addressed the very issues raised in this rejection. The submission of such a declaration in this case may be persuasive to overcome the instant rejection.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Keiback *et al.* (US 5645995).

Kieback *et al.* teach a method for screening a patient for cancer or precancer, the method comprising the step of detecting in a patient tissue or body fluid sample comprising exfoliated cells a nucleic acid fragment of a length that is greater that a length of a nucleic acid expected to be present in said sample in a healthy patient, the presence of said fragment being a positive screen for cancer or precancer.

Kieback *et al.* teach an assay for the detection of nucleic acids having an Alu insertion in INTRON G of the human progesterone receptor gene, thus Keiback *et al.* are teaching a method for detecting a nucleic acid with a greater length than that expected to be in the healthy patient since the at risk patient has the insertion in their DNA (Col. 11-12, and claim 3, for example).

8. Claims 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Ditkoff *et al.* (Surgery, 1996, Volume 120, Number 6, 959-965).

Ditkoff *et al.* teach a method for screening a patient for cancer or precancer, the method comprisign the steps of :

detecting in a patient tissue of body fluid sample comprising exfoliated cells and cellular debris (blood) whether an amount of nucleic acid greater than 200 base pairs in length exceeds a predetermined amount; identifying a positive screen for cancer or precancer if said amount does exceed said predetermined amount (p. 960-961).

The method taught by Ditkoff *et al.* comprises conducting an amplification reaction designed to amplify only nucleic acids in said sample that are 529 bp (Fig. 2A).

In the method taught by Ditkoff *et al.*, the "predetermined amount" is zero. When Ditkoff *et al.* detect an amount of the target nucleic acid that is greater than the predetermined amount, the screen is considered positive.

9. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Smith-Ravin *et al.* (Gut 1995; 36:81-86).

Smith-Ravin *et al.* teach a method for screening a patient for cancer or precancer, the method comprising the steps of :

detecting in a patient tissue of body fluid sample comprising exfoliated cells and cellular debris (stool), whether an amount of nucleic acid greater than 200 base pairs in length exceeds a predetermined amount; identifying a positive screen for cancer or precancer if said amount does exceed said predetermined amount (p. 83-84). It is noted that the amplification product detected in the methods of Smitn-Ravin *et al.* are smaller than 200 base pairs, however these products are merely a representation of a larger genomic fragment in the sample, that is the genomic DNA that comprises the fragment. They are used as an indication of the larger fragment, and thus this is a method for detecting the presence of the larger fragment. The fragment detected by Smith-Ravin *et al.* is not expected to be in healthy patients, thus the predetermined amount is zero.

Smith-Ravin *et al.* further teach the enriching and isolation of human DNA in the sample via centrifugation and then extraction (p. 82-83).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 6143529. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the 6143529 represent a species which falls within the broad genus of the instantly claimed invention.

Response to Remarks

Applicant argues that the Ditkoff *et al.* reference fails to teach or suggest a method for detecting cancer or precancer based solely on the length, not identity of nucleic acids. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a method which detects based solely on length) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim rejected over Ditkoff *et al.* is sufficiently broad so as to encompass the teachings of Ditkoff *et al.*, as discussed in the rejection above. The arguments concerning Smith-Ravin *et al.* are essentially duplicative of those concerning Ditkoff *et al.* and are addressed above in the response to remarks and in the rejection over Smith-Ravin *et al.*

The rejections over Shiff *et al.* are withdrawn. Shiff *et al.* teach a method in which percentage rations of apoptotic cells or those with DNA fragmentation in colorectal mucosal crypts to the total number of cells is used as an indicator of cancer or precancer. However, Shiff *et al.* fail to teach or suggest a method wherein the a ratio is provided between the amount of DNA over 200 base pairs and the amount of DNA less than 200 base pairs in a given sample is an indicator of cancer or precancer. The prior art does not specifically teach or suggest such a method. Thus, the rejection over Schiff *et al.* is withdrawn.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

November 14, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600